

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03318

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C12N15/85	C12N15/12	C12N15/19	C07K14/47	C07K14/52
	C12N15/58	C12N9/72	C12N15/53	C12N9/02	C12N15/23
	C07K14/57	C12N15/16	C07K14/58	C12N5/10	A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K C12Q A01K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 17359 A (REGENTS OF UNIVERSITY OF CALIFORNIA (US); WILLIAMS L.; MORISHITA K.) 15 May 1997</p> <p>see abstract see page 2, line 32 - page 3, line 7 see page 45, line 4-31 see page 53 - page 59; claims</p> <p style="text-align: center;">--- -/--</p>	<p>1,4,10, 12,14, 16-18, 20-22, 25,40</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

23 October 1998

Date of mailing of the international search report

11/11/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Macchia, G

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International Application No

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IPC 6 C12Q1/68 A01K67/027 G01N33/50 A61K35/00

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A	<p>RÖNICKE V ET AL: "Characterization of the endothelium-specific murine vascular endothelial growth factor receptor-2 (Flk-1) promoter"</p> <p>CIRCULATION RESEARCH, vol. 79, no. 2, August 1996, pages 277-285, XP000604137</p> <p>cited in the application</p> <p>see page 279, right-hand column, line 6-7</p> <p>see page 280; figure 2</p> <p>see page 282; figure 5B</p> <p>see page 283, left-hand column, line 3-9</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1,2



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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SCHLAEGER T.M. ET AL.: "Uniform vascular-endothelial-cell -specific gene expression in both embryonic and adult transgenic mice" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, April 1997, pages 3058-3063, XP002081315 cited in the application see abstract</p>	1,2
A	<p>JORCYK C.L. ET AL.: "Multiple regulatory regions control the expression of Ets-1 in the developing mouse: vascular expression conferred by intron 1" CELLULAR AND MOLECULAR BIOLOGY, vol. 43, no. 2, March 1997, pages 211-225, XP002081894 cited in the application see abstract</p>	1,2
A	<p>PATTERSON C. ET AL.: "Cloning and functional analysis of the promoter for KDR/flk-1, a receptor for vascular endothelial growth factor" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 39, 29 September 1995, pages 23111-23118, XP002081230 cited in the application</p>	
A	<p>QUANDT K. ET AL.: "MatInd and MatInspector: new fast and versatile tools for detection of consensus matches in nucleotide sequence data" NUCLEIC ACIDS RESEARCH, vol. 23, no. 23, 1995, pages 4878-4884, XP002081231 cited in the application</p>	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/03318

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 34, 35 and 39
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/EP 98/03318



5- 53745 + 310 (patent family: none) (44: 1000)

PCT

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C 1822 PCT		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION	
International application No. PCT/EP98/03318	International filing date (day/month/year) 03/06/1998	Priority date (day/month/year) 03/06/1997	
International Patent Classification (IPC) or national classification and IPC C12N15/85			
Applicant MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 6 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input checked="" type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 24/11/1998		Date of completion of this report	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465		Authorized officer Herrmann, K Telephone No. (+49-89) 2399 2670 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/03318

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-72 as originally filed

Claims, No.:

1-40 as received on 04/06/1999 with letter of 04/06/1999

Drawings, sheets:

1/21-21/21 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
 - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/03318

been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 34, 35, 39, 40.

because:

- ☒ the said international application, or the said claims Nos. 34, 35, 39, 40 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/03318

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19, 23-25, 29-33, 36-38
	No:	Claims	1-18, 20-22, 26-28
Inventive step (IS)	Yes:	Claims	19, 23-25, 29-33, 36-38
	No:	Claims	1-18, 20-22, 26-28
Industrial applicability (IA)	Yes:	Claims	1-33, 36-38
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/03318

Re ITEM I (Basis of the opinion)

The amended claims 1-40 filed with letter of 04.06.99 can be regarded as meeting the requirements of Art. 34(2)(b) PCT.

Re ITEM II (Priority)

The priority document pertaining to the present application was not available at the time this international preliminary examination report (IPER) was established. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (03.06.97).

Re ITEM III (Non-establishment of opinion)

As far as the subject-matter of claims 34, 35, 39 and 40 is directed to *in vivo* methods, it is also directed to methods for treatment of the human or animal body and thus, excluded from examination by Art. 34(4)(a)(i) PCT in combination with Rule 67.1(iv) PCT.

No unified criteria exist among the PCT member states for the assessment whether the treatment of the human or animal body is industrially applicable or not. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re ITEM V (Novelty, inventive step, industrial applicability)

1 Summary of the present application

The present application is related to the Flk-1 gene (fetal liver kinase-1/kinase-insert domain-containing receptor/VEGF-receptor 2). Flk-1 is a receptor for the endothelial mitogen VEGF (vascular endothelial growth factor). Through

interaction with Flk-1, VEGF plays critical roles in growth and maintenance of vascular endothelial cells and in the development of new blood vessels. More specifically, the application is related to a 510 bp regulatory sequence in intron 1 of the Flk-1 gene (Fig. 12: "Flk-1 intron enhancer"; nucleotides 10094-10608 of SEQ ID NO:1). The application is also related to various uses of said regulatory sequence.

2 Citations

The documents mentioned in this IPER are numbered as in the international search report dated 23.10.98, i.e. D1 corresponds to the first document of the search report etc.

3 Novelty (Art. 33(2) PCT)

- 3.1 The subject-matter of claims 19, 23-25, 29-33 and 36-38 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel.
- 3.2 The subject-matter of claims 1-18, 20-22 and 26-28 does not meet the requirements of Art. 33(2) and 33(3) PCT.
- 3.3 **D3** (Schlaeger, T.M. et al.) discloses an endothelium-specific enhancer in the first intron of the murine *TIE2* gene (see abstract and Fig. 4 of D3). Since no degree of homology is given in claim 1 (cf. description p. 8, l. 9-11), the enhancer of **D3** is regarded as novelty destroying for the subject-matter of claim 1. Genes/proteins can have a common evolutionary origin and still exhibit distinct properties. In the case of Flk-1 and TIE-2 there even is a strong indication for some common evolutionary origin: A significant amino acid sequence similarity can be found in the intracellular tyrosine kinase domain of the Flk-1 gene and the TIE-2 gene. Besides, a particular product's origin cannot be used to establish novelty of the product *per se*.

- 3.4 In view of the novelty-objection raised under **item V, 3.3**, the further embodiments in claims 2-18, 20-22 and 26-28 are also not novel over the subject-matter disclosed in **D3** (also cf. **item VIII**).

4 Inventive step (Art. 33(3) PCT)

The subject-matter of claims 19, 23-25, 29-33 and 36-38 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Art. 33(3) PCT.

5 Industrial applicability (Art. 33(4) PCT)

Claims 1-33 and 36-38 meet the criteria as set forth by Art. 33(4) PCT.

Re ITEM VIII (Certain observations on the international application)

- 1 The present application contains such a high number of independent claims (17 out of 40) that the application as a whole lacks conciseness (Art. 6 EPC). Claims directed to the same category should be made dependent upon each other to meet the requirements of Art. 6 PCT (e.g. claims 29-32, claims 36-38, claims 24 and 25).
- 2 Concerning the claims directed to the regulatory DNA sequence of present application (e.g. claim 1), attention is drawn to Rule 6.3(a) PCT. Said Rule requires that the matter for which protection is sought be defined in terms of technical features of the invention (also cf. PCT Guidelines III-4.4, as in force from 09.10.98). A DNA molecule is a chemical compound which can be clearly and unambiguously defined by its chemical structure, i.e., its nucleic acid sequence.
- 3 The same objection (**item VIII, 2**) applies to claim 3(f) wherein the expression "a fragment, analogue or derivative capable of conferring expression in endothelial cells in vivo" renders the scope of e.g. claim 3(f) unclear (Art. 6 PCT). It is completely open to interpretation which fragment, analogue or derivative, i.e. which sequences fall under the scope of said claim.

**INTERNATIONAL PRELIMINARY
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- 4 General references to "hybridization" (e.g. claims 3(d) and 9(c)) without clearly specifying any further requirement of the nucleic acid to be hybridized are ambiguous and thus unclear for the following reasons: (i) The isolated nucleotide can be as short as 5 or 10 nucleotides (the claim does not require that said polynucleotide capable of hybridizing encodes anything. (ii) The word comprising implies the presence of further unrelated sequences. The scope of the claim is not clearly defined as far as the claimed isolated nucleic acids could well hybridize with said unrelated sequence but not with a regulatory or a promoter sequence, respectively (Art. 6 PCT).

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference C 1822 PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 98/ 03318	International filing date (day/month/year) 03/06/1998	(Earliest) Priority Date (day/month/year) 03/06/1997
Applicant MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).
2. ☐ **Unity of invention is lacking** (see Box II).
3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☒ filed with the international application.
 - ☐ furnished by the applicant separately from the international application.
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the **title**, ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
 - ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:
 - Figure No. — ☐ as suggested by the applicant. ☐ None of the figures.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.

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Remark on Protest

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Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Macchia, G

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"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Macchia, G

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 98/03318

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHLAEGER T.M. ET AL.: "Uniform vascular-endothelial-cell -specific gene expression in both embryonic and adult transgenic mice" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, April 1997, pages 3058-3063, XP002081315 cited in the application see abstract ---	1,2
A	JORCYK C.L. ET AL.: "Multiple regulatory regions control the expression of Ets-1 in the developing mouse: vascular expression conferred by intron 1" CELLULAR AND MOLECULAR BIOLOGY, vol. 43, no. 2, March 1997, pages 211-225, XP002081894 cited in the application see abstract ---	1,2
A	PATTERSON C. ET AL.: "Cloning and functional analysis of the promoter for KDR/flk-1, a receptor for vascular endothelial growth factor" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 39, 29 September 1995, pages 23111-23118, XP002081230 cited in the application ---	
A	QUANDT K. ET AL.: "MatInd and MatInspector: new fast and versatile tools for detection of consensus matches in nucleotide sequence data" NUCLEIC ACIDS RESEARCH, vol. 23, no. 23, 1995, pages 4878-4884, XP002081231 cited in the application -----	

In **con** on patent family members

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